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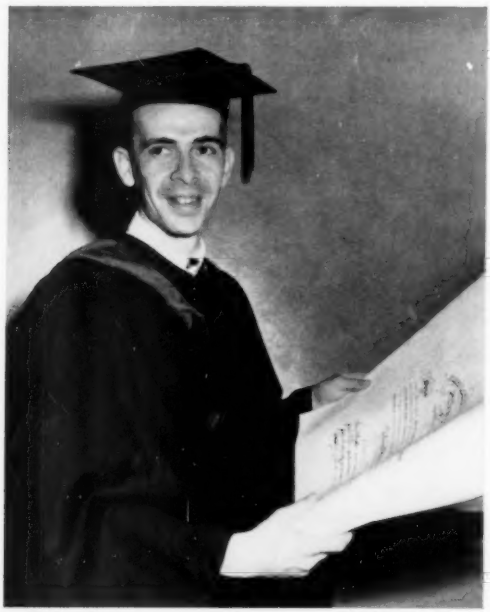

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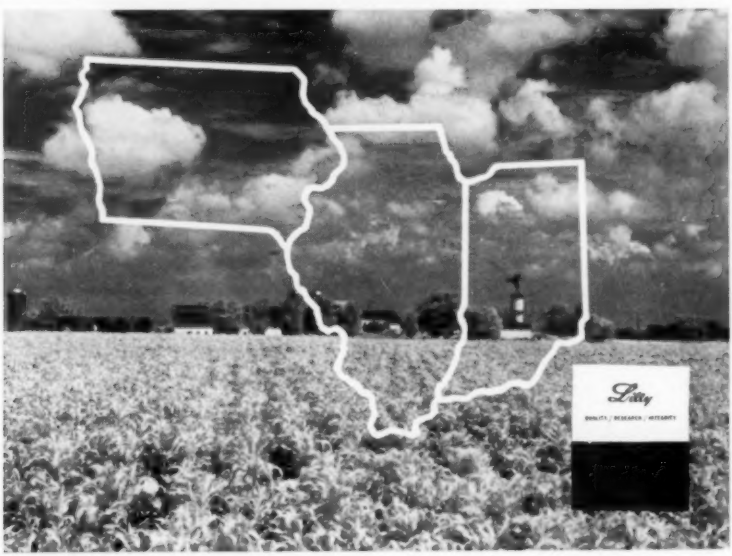

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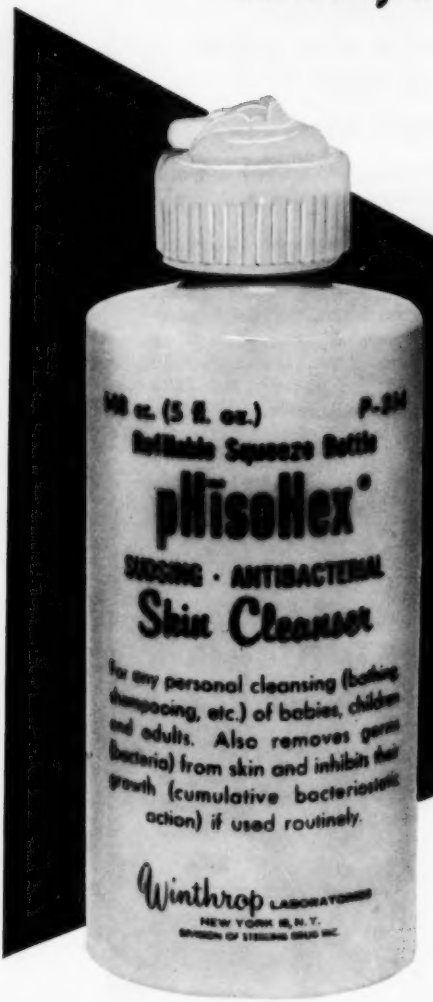

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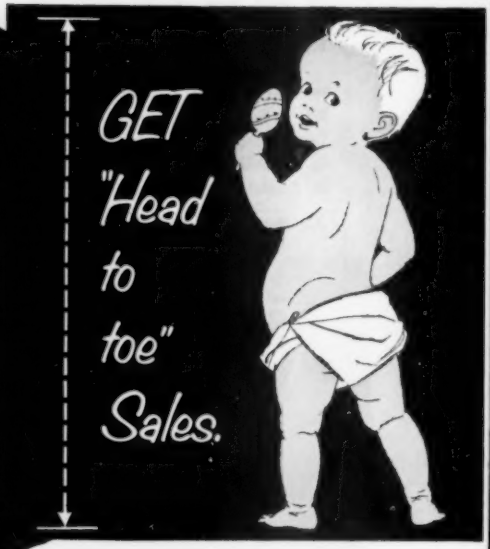

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E D I T O R I A L

A CHANGING PHILOSOPHY

AS one reflects on the nature of current events and tries to put them in proper perspective, it is difficult not to be somewhat pessimistic concerning the future. Americans only too often are inclined to consider Nikita Khrushchev as a bungling, little fellow who visits capitals behind the Iron Curtain, as a sort of Communist ambassador of good will, not posing any serious hazard to the safety and security of the Western world. To suggest that Premier Khrushchev may indeed have a keener insight into our true weakness as a nation than we have ourselves engenders the risk of being accused as a Communist sympathizer. Some of his off-the-cuff comments concerning our country make it appear that he does know more about us than we suspect. In fact, a recent remark of his may have pointed a discerning finger at what may prove to be the source of our undoing. In commenting to a group of visiting American businessmen, Khrushchev made the observation that they need not fear an atomic attack directed against the United States by Russia. He advised them that it would be more important for them to take care that their grandchildren do not embrace the philosophy of Communism. While this statement was probably read in our newspapers by many and considered a huge joke, it is in fact terribly serious. The philosophy of Americans is gradually undergoing a transition wherein collectivism and state paternalism seem only too often to be considered as a part of our so-called liberal thought and economic philosophy. Perhaps it is inevitable that, as our population grows rapidly and our economic resources dwindle, some sort of state socialism cannot be avoided. On the other hand, we still seem to give lip service to individual initiative and the private enterprise system. These are soundly endorsed except when it comes to making the effort itself. Here, it is only too common for each of us to turn to the federal government asking that it take care of all our needs including economic security, education, medical care, and all of the other things which in the past individuals have

considered as their own responsibility. There are even some now in Congress who presumably consider profit on the part of business as evil and suggest that no price should be raised without the express consent of government. Although World War II has been over for more than a decade, rent controls are still in effect in many places in spite of the fact that there are no controls on wages. One cannot escape the conviction that this is basically because there are more people who rent homes than there are landlords. Therefore, rent controls, even though they violate property rights are maintained because they are politically expedient. Many of our labor unions are becoming more and more contemptuous of both management and the ownership of the means of production. It must be obvious to one who studies the situation that the only change in ownership which can occur is for it to be assumed by government. We then have state socialism. With such a change, government might easily fall under the control of some of our present labor leaders since they would be in the most strategic position to assume power. When the jockeying for power and position was over, there would be little difference between the system which would obtain here and that in present-day Russia.

This continuing trend toward collectivism is difficult to reverse since everyone in the United States today seems determined to get something for nothing and firmly believes that the government can give them this. To the degree that we continue to rely on government, we risk losing that economic system and social philosophy of which we boast. Government itself cannot be blamed for giving the people what they ask. In a sense, this is its function and the politician who does not try to meet the wishes of his constituents will not last long. Krushchev's admonishment was not a jest but a keen observation based upon a still keener insight into our domestic affairs. It is ironic that we are spending millions to protect ourselves against atomic conquest by Russia while we show not the slightest concern about those tendencies on the part of our people which promise to bring us someday into "happy" union with world Communism.

L. F. Tice

THE FORMULATION AND EVALUATION OF ENTERIC COATED ASPIRIN TABLETS *

By R. H. Blythe, G. M. Grass, and D. R. MacDonnell

An aspirin tablet with an enteric coat of cellulose acetate phthalate and hydroabietyl alcohol in a ratio of 2 to 1 has been formulated which will resist simulated gastric fluid for at least 4 hours and will disintegrate in simulated intestinal fluid in less than one-half hour in a U. S. P. disintegration apparatus. In addition, the tablet will produce blood concentrations equal to those produced by plain aspirin. The in vitro *and human* in vivo *studies on this product are described.*

THIS paper reports research undertaken to develop an enteric coated aspirin tablet which would enable patients who suffer gastric irritation with plain aspirin to tolerate large doses over a long period of time and which would produce blood concentrations as high as those produced by plain aspirin. Tests were done in humans to establish the length of time most of the tablets remain in the stomach and the length of time they take to disintegrate after passing through the stomach. *In vitro* tests were developed to assure the reproduction of disintegration characteristics of each batch of tablets, and to determine their *in vitro* disintegration time and their chemical stability. Guar gum, shown by Eatherton *et al.* (1) to be superior to starch as a disintegrant in some compressed tablets, was compared with corn starch in 10 per cent concentrations to determine its relative efficacy as a disintegrant in enteric coated aspirin.

Literature reviews (2, 3) on enteric coatings usually describe the composition of coatings and/or *in vitro* disintegration tests devised to evaluate them. However, *in vitro* tests alone cannot be used to predict the clinical usefulness of a product. Only tests done in humans can determine the value of a product in humans. After first determining the behavior of a product in humans, one can then develop a

* From the Research and Development Division of Smith Kline & French Laboratories, Philadelphia, Penna.

suitable *in vitro* test to make certain that each succeeding batch has the same properties as those of the product which proved to be clinically satisfactory. It is hoped that this report will stimulate others to publish *in vivo* as well as *in vitro* data so that eventually enough data will be available to formulate some general correlation between *in vitro* and *in vivo* behavior of products.

Experimental

Formulation of Tablet

Two compressed tablet formulations, one with corn starch as the disintegrant and the other with guar gum as the disintegrant, were used in the various *in vitro* and *in vivo* studies. Similar results were obtained with small and large sized batches; for example, 5,000 and 250,000 tablets per batch. The coating was first developed for the corn starch-containing granulation, but these tablets were found to disintegrate more slowly upon aging, and the coating was then used on the guar gum-containing granulation.

The starch-containing formulation was made with a 12 mesh (all through a U. S. standard 12 mesh screen) commercial aspirin granulation produced by a slugging process, and contained 10 per cent corn starch. The guar gum formula consisted of 90 per cent of 40 mesh crystalline aspirin and 10 per cent of 100 mesh guar gum [1] mix. Using a Stokes Model B rotary press, ⅜ inch deep convex tablets were formed without additional granulation, and were compressed to a hardness of 5 kg. as measured with a Monsanto Hardness Tester. The compressed tablets were given 3 "sealing and rounding" coats, each consisting of a layer of gelatin-syrup adhesive solution and acacia dusting powder, the tablets being dried in the pans between coats and then dried overnight in trays at 50° C. after the last coat. About 20 coats of cellulose acetate phthalate:hydroabietyl alcohol coating solution [2] were applied. The quantity may vary somewhat from batch to batch, but must be sufficient to prevent penetration of U. S. P. simulated gastric fluid when the tablets are immersed in it for 4 hours and, at the same time, allow disintegration in U. S. P. simulated

[1] Jaguar A-20-B grade (between 100 and 200 mesh), a brand and grade produced by Stein, Hall & Company, Inc., New York City.

[2] Cellulose acetate phthalate, 20 per cent; hydroabietyl alcohol, 10 per cent; acetone, 30 per cent; alcohol, 35 per cent; and n-propyl alcohol, 5 per cent.

intestinal fluid within one-half hour. This usually amounts to about 40 mg. of solvent-free coating material per tablet. A conventional sugar coating was applied to the tablet as a finishing coat.

In vivo Studies

Three radiographic studies were conducted on volunteers to determine the emptying time of the stomach and the *in vivo* disintegration rate of the tablets. Each volunteer took 3 tablets made radiopaque with a thin layer of barium sulfate (about 100 mg./tablet) under the enteric coating. These tablets had the same *in vitro* disintegration characteristics as the tablets that were not radiopaque. The tablets were followed by means of radiographs. In studies B and C, radiographs were taken at 15-minute intervals for the first hour and then at 30-minute intervals until the tablets distintegrated or until 7 hours had elapsed. The 30-minute observation was omitted during the lunch period. In the initial study (A), the radiographs were not taken exactly at 30-minute intervals. In study A, the 23 volunteers took the tablets 2 hours after breakfast. In study B, the 5 volunteers took the tablets on an empty stomach 15 minutes before breakfast. In study C, the 5 volunteers took the tablets one hour after breakfast. From the radiographs, it was possible to determine the length of time required for the tablets to leave the stomach and the time required for them to disintegrate. In reading the radiographs, the tablets were assumed to have left the stomach at the midpoint between the last time they were observed to be present and the first time they were observed to be out of the stomach.

Absorption studies were done on 10 arthritic patients who took 3 tablets 4 times a day (total daily dose of aspirin, 3.888 Gm.). Each patient received plain aspirin and enteric coated guar gum-containing aspirin tablets, separately, for periods of 7 days each. The blood salicylate levels were determined by the Brodie method (4). Blood samples were taken by venipuncture the last 3 mornings and the last 5 evenings, just before administration of the morning or evening dose, of each 7-day regimen.

The completeness of *in vivo* disintegration was studied by a fecal test. Each of 20 volunteers took 8 tablets a day for 5 days and collected all feces until 24 hours after the last dose. All incompletely disintegrated tablet remnants were carefully separated from the feces,

rinsed, dried, and weighed. Both fresh and aged starch-containing tablets were tested this way. Guar gum-containing tablets were tested only on the subjects who previously had passed some incompletely disintegrated remnants of the starch-containing tablets.

In vitro Studies—Disintegration and Stability

The stability of the tablet was studied by following the change in disintegration time and the per cent of hydrolysis upon aging. A modified U. S. P. XV disintegration test was used; the sample size being increased, the time in simulated gastric fluid increased, and the time in simulated intestinal fluid decreased. One hundred fifty tablets were placed in individual tubes of a specially designed basket having the regular 10 mesh screen in the bottom. This was raised and lowered 28-30 times per minute in U. S. P. simulated gastric fluid at 37° ± 2° C. for 4 hours. The tablets were examined, and the number noted that showed any evidence of disintegration in the simulated gastric fluid. The tablets were then placed in U. S. P. simulated intestinal fluid at 37° ± 2° C. and the agitation continued for a period up to 2 hours, noting the time that each tablet completely passed through the screen and the per cent of composite residue, if any, on the screen at the end of the 2 hour period.

Hydrolysis was determined by a two-component spectrophotometric assay for aspirin and salicylic acid (hydrolysis product), using chloroform as the solvent. Aspirin was read at 277 millimicrons and the salicylic acid at 307 millimicrons, and the quantities calculated using simultaneous equations.

Results

In vivo Studies

The x-ray studies revealed that there is a wide range of time over which tablets will pass from the stomach, from less than one-half hour to over 7 hours. In the study involving 23 subjects (A), approximately one-half of the tablets had left the stomach about 1.6 hours after ingestion. About one-half of the tablets left the stomach slightly sooner when taken on an empty stomach (study B), and nearly all the tablets left the stomach more slowly when taken one hour after breakfast (study C, Fig. 1). When several tablets are taken at one time, they are more likely to leave the stomach one or two at a time than all together (Fig. 2).

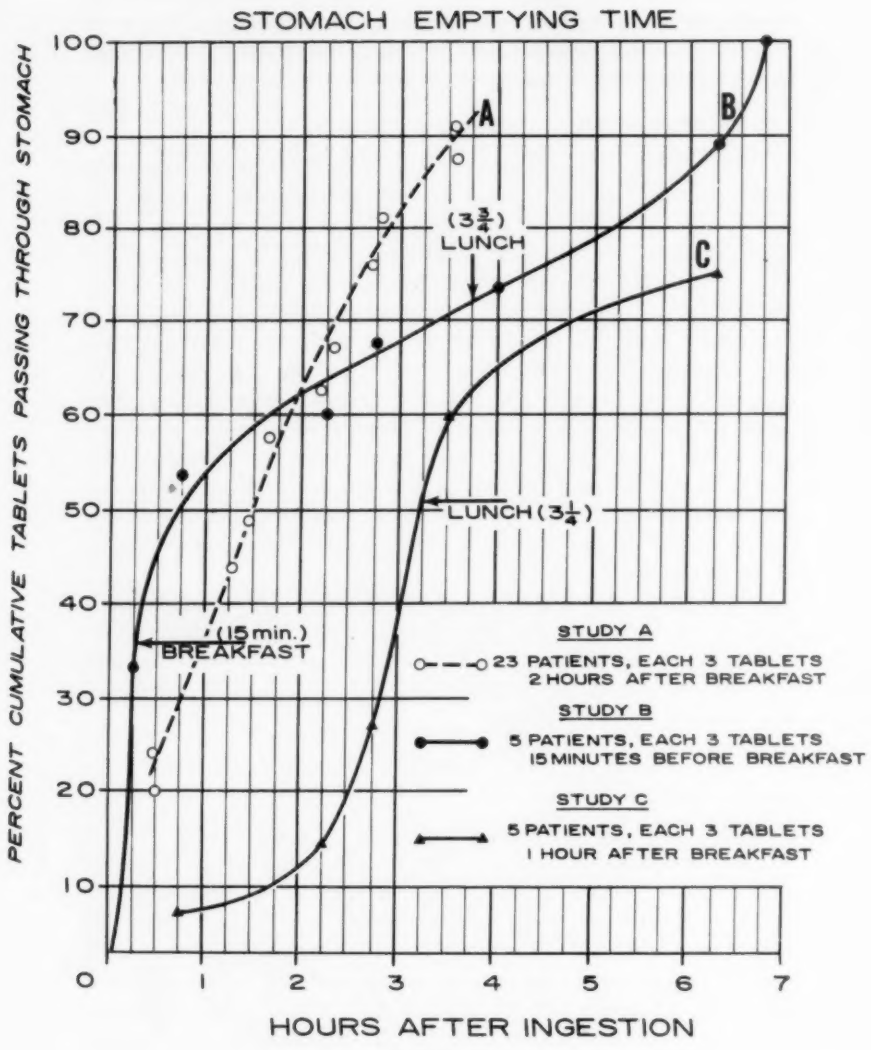
STOMACH EMPTYING TIME
PERCENT CUMULATIVE TABLETS PASSING THROUGH STOMACH
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
HOURS AFTER INGESTION
A
B
C
(3¾) LUNCH
LUNCH (3¼)
(15 min.) BREAKFAST
STUDY A
23 PATIENTS, EACH 3 TABLETS
2 HOURS AFTER BREAKFAST
STUDY B
5 PATIENTS, EACH 3 TABLETS
15 MINUTES BEFORE BREAKFAST
STUDY C
5 PATIENTS, EACH 3 TABLETS
1 HOUR AFTER BREAKFAST

FIGURE 1

Tablets taking less than 2 hours to leave the stomach showed an average disintegration time of 2.1 hours in the intestinal tract, while those taking over 2 hours to leave the stomach took an average of only 1.3 hours to disintegrate after leaving the stomach (Fig. 2).

Patients vary greatly in their ability to absorb aspirin, achieving free salicylate blood concentrations of from about 12 to over 31 mg. per cent. Patients show comparable blood levels with either the plain or the enteric coated aspirin, except that the blood salicylate level is distinctly higher in the morning when the patients are on the enteric aspirin regimen, giving a 24.7 mg. per cent concentration with the enteric coated aspirin and 17.6 mg. per cent concentration with plain aspirin (Table I).

The tablets with starch as the disintegrant showed poorer *in vivo* disintegration upon aging, with as many as 16 out of 20 volunteers passing some incompletely disintegrated remnants of the 18-month-old tablets. However, the undisintegrated portions of the 10 per cent of the tablets passed represented less than 2 per cent of the total medicament ingested (Table II). No remnants of the tablets made with guar gum were recovered from any of the feces, although the guar gum tablets were taken by volunteers who had previously passed starch-containing tablets.

In vitro Results

The tablets made with starch showed a marked and rather irregular degree of increased *in vitro* disintegration time upon aging, while the average increase shown by the guar gum-containing tablets was small and spread over a narrower range (Table III).

The amount of hydrolysis that developed in either formula upon aging was relatively small and may be considered insignificant (Table IV).

Discussion

The amount of food in the stomach appears to have an effect upon the rate of passage of tablets from it; at least, more tablets appear to pass more quickly from an empty or nearly empty stomach. It would seem desirable for the physician to prescribe how long before or after meals he wishes his patient to take tablets to get the most consistent results.

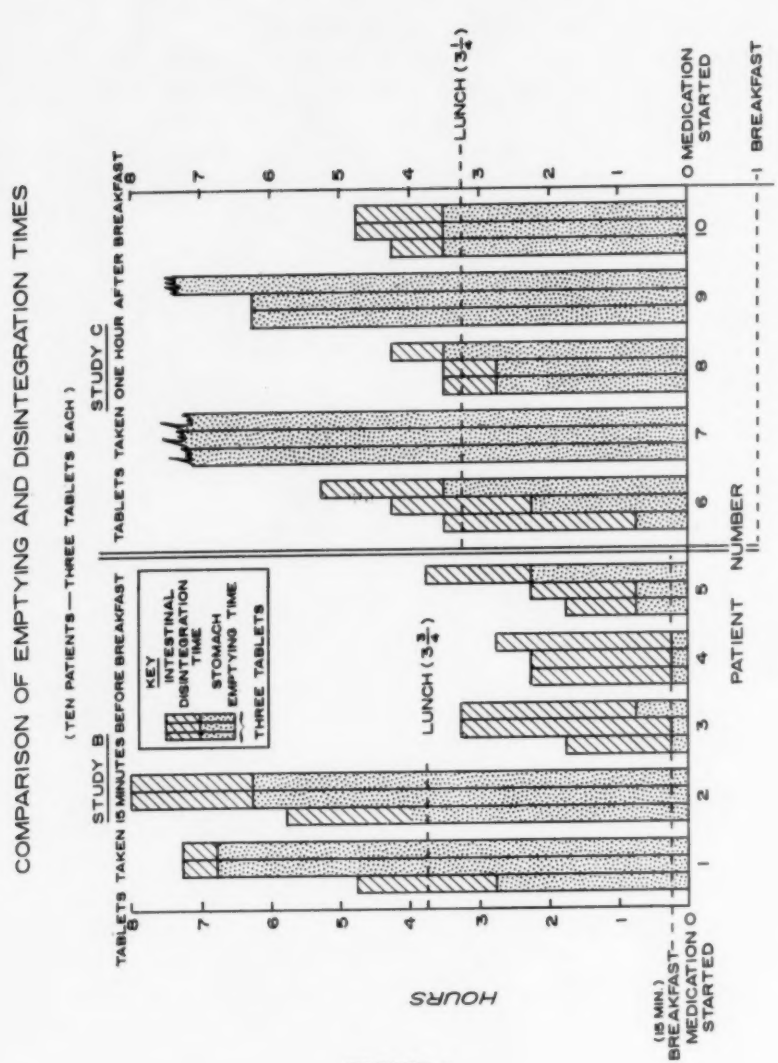
COMPARISON OF EMPTYING AND DISINTEGRATION TIMES
(TEN PATIENTS—THREE TABLETS EACH)
STUDY B
TABLETS TAKEN 15 MINUTES BEFORE BREAKFAST
STUDY C
TABLETS TAKEN ONE HOUR AFTER BREAKFAST
KEY
INTESTINAL DISINTEGRATION TIME
STOMACH EMPTYING TIME
THREE TABLETS
LUNCH (3¾)
LUNCH (3¾)
HOURS
PATIENT NUMBER
(15 MIN.) BREAKFAST—MEDICATION STARTED
O MEDICATION STARTED
-1 BREAKFAST

FIGURE 2

TABLE I

BLOOD CONCENTRATION—PLAIN VS. ENTERIC COATED ASPIRIN

(Expressed as mg. per cent free salicylate)

Patient	Form of Aspirin	3rd-day P. M.	4th-day P. M.	5th-day A. M.	5th-day P. M.	6th-day A. M.	6th-day P. M.	7th-day A. M.	7th-day P. M.	Average
AD	Plain	18.56	11.60	9.28	11.60	9.28	12.76	10.44	15.08	12.325
	Enteric	13.92	11.60	17.40	13.92	17.40	11.60	13.92	11.60	13.920
CS	Plain	33.64	30.16	27.84	30.72	26.04	34.96	31.32	32.48	30.895
	Enteric	30.80	33.64	35.96	30.16	34.80	35.96	33.64	34.80	34.220
FH	Plain	16.24	18.56	16.24	19.72	11.60	19.72	12.76	22.04	17.110
	Enteric	25.52	20.88	27.84	16.24	22.04	18.56	22.04	20.88	21.750
LK	Plain	26.68	20.88	16.24	26.68	17.40	23.20	16.24	22.04	21.170
	Enteric	27.00	20.88	25.52	22.04	26.68	16.24	22.04	15.08	21.935
MS	Plain	32.88	30.16	31.32	37.28	26.84	33.64	24.36	34.80	31.410
	Enteric	32.48	31.32	35.96	35.96	33.64	25.52	33.64	26.68	31.895
RM	Plain	18.56	18.56	11.60	12.24	12.76	19.72	13.92	19.72	16.010
	Enteric	20.88	15.08	20.88	17.40	27.84	18.56	20.88	15.08	19.575
BK	Plain	25.52	22.04	23.20	27.84	20.04	26.84	25.52	30.16	25.145
	Enteric	23.20	15.08	31.32	24.36	26.68	20.88	22.04	24.36	23.490
TS	Plain	23.20	25.52	19.72	19.72	18.56	22.04	19.72	26.68	21.895
	Enteric	23.20	18.56	25.52	22.04	22.04	18.56	27.84	18.56	22.040
BJ	Plain	19.72	15.08	11.60	18.54	16.24	17.40	11.60	16.24	15.803
	Enteric	18.56	15.04	20.88	16.24	20.88	18.56	16.24	16.24	17.830
JW	Plain	16.24	11.60	9.28	13.92	10.44	13.08	11.60	13.92	12.510
	Enteric	19.72	20.88	20.88	17.40	17.40	22.04	18.56	16.24	19.140
Averages	Plain	23.120	20.410	17.630	21.920	16.920	22.340	17.750	23.320	20.426
	Enteric	23.930	20.300	26.220	21.580	24.940	20.650	23.080	19.950	22.581

Composite Average (10 subjects)	*Mornings*	*Evenings*
Plain aspirin	17.6	20.6
Enteric coated aspirin	24.7	21.3

The variation of emptying time, particularly of individual tablets, might be explained by the anticipated physiologic emptying of the stomach described by Ivy (5) who states that the greater portion of the meal is held in the "hopper" or fundic portion of the stomach where there is little mixing or other motion. Ivy also noted that the portion expelled is chiefly the thinner material, and that large lumps "bounce" back into the stomach when they reach the pyloric sphincter. An examination of the radiographs reveals that several tablets are frequently near the pyloric sphincter while, in subsequent pictures in the same series, some or all of the tablets will be resting in the lower fundic portion of the stomach more remote from the sphincter. Therefore, the authors believe that undisintegrated tablets act like lumps of food and also frequently "bounce".

Since tablets remain in the stomach for variable, but relatively long periods, it seemed reasonable that an *in vitro* specification should require that tablets resist attack by simulated gastric fluid for at least 4 hours. Tablets that are resistant for 4 hours will generally continue to be resistant to stomach fluids for a much longer period as shown by the *in vivo* radiographic studies.

TABLE II

DATA ON FECAL TESTS FOR PASSAGE OF TABLETS

Disintegrant	*Starch*			*Guar Gum*	
Age of Tablets	*Fresh*	*12 Mo.*	*18 Mo.*	*Fresh*	*3 Mo.*
No. of Subjects Passing Tablets	9/20	11/20	16/20	0/6 Note 1	0/6 Note 2
% of Tabs Taken Showing Some Remnants in Feces	3	7	10		
% Active Drug Passed	0.3	0.7	2.0		

Note 1—6 subjects used had passed 43/240 in 12 mo. old "starch tablet" test.

Note 2—6 subjects used had passed 59/240 in 18 mo. old "starch tablet" test.

TABLE III

IN VITRO DISINTEGRATION TIME

Minutes in Intestinal Fluid (after 4 hours in Gastric Fluid)

Disinte-	*Original*			*6 Mo.*			*12 Mo.*			*18 Mo.*		
grant	*Min.*	*Max.*	*Av.*	*Min.*	*Max.*	*Av.*	*Min.*	*Max.*	*Av.*	*Min.*	*Max.*	*Av.*
Starch	7	16	9	12	112	44	11	149	78	8	155	35
Guar Gum	9	18	11	11	17	14	13	22	16	9	25	17

TABLE IV

ASPIRIN STABILITY

PER CENT HYDROLYSIS

Disintegrant	*Original*	*6 Mo.*	*12 Mo.*	*18 Mo.*
Starch	0.	0.3	0.8	0.6
Guar Gum	0.14	0.6	1.2	0.7

Clinical confirmation of the resistance of this coating to gastric release is given by Sprecher (6) who found that 31 of the 32 patients known to be aspirin intolerant could take these tablets without discomfort. Introcaso (7) found that 41 of another series of 42 patients who had varying degrees of gastric irritation to plain aspirin could daily take 3.24-5.83 Gm. of aspirin in the form of this enteric coated tablet without gastric disturbance.

The radiopaque tablets had the same resistance to simulated gastric fluid and the same *in vitro* disintegration time in simulated intestinal fluid (less than one-half hour) as the non-radiopaque tablets. Their disintegration time after leaving the stomach, as interpreted from serial radiographs, ranged from one-half hour to 3 hours with an average of 1.6 hours. It is reasonable to assume that the non-radiopaque tablets had similar *in vivo* disintegration. The fact that each of the 10 patients showed comparable blood levels, based on the average of 8 determinations each, indicates good absorption of aspirin well down in the intestine.

In addition to eliminating gastric irritation, the enteric coating also delays the release of the night dose of aspirin so that the blood salicylate concentration is at or near its peak in the morning. This is believed to account for the superior relief from pain that the majority

of patients observed in the morning when on the enteric coated aspirin regimen.

Although the approximately 2 per cent of incompletely disintegrated drug which was passed in the feces with the 18-month-old starch-containing tablets was not considered clinically significant, the fact that the tablets showed a marked increase in disintegration time upon aging and that some incompletely disintegrated tablet remnants of fresh tablets were passed led us to decide to develop a tablet that would not possess these drawbacks. Several formulas were made and tested. The one containing 10 per cent guar gum as the disintegrant appeared to be the most satisfactory of these (and so was the only one on which all tests were done).

Tablets made with starch disintegrant that show a longer *in vitro* disintegration time upon aging also show a greater failure to completely disintegrate *in vivo*. However, guar gum-containing tablets, having approximately the same *in vitro* disintegration as new starch-containing tablets, appeared to disintegrate completely *in vivo* while those made with starch did not. Much more *in vitro* and *in vivo* data will undoubtedly have to be obtained on various active ingredients, disintegrants, and coatings before one can make generalizations and broad correlations between *in vitro* and *in vivo* tests.

Acknowledgments

We wish to thank Drs. J. H. Vastine, 2nd. and G. P. Keefer of Philadelphia for the radiological studies, Drs. E. K. Clardy and C. A. Sloan of the Leo N. Levi Memorial Hospital, Hot Springs, Arkansas, for the salicylate blood level studies, and Dr. P. U. Weaver of Temple University School of Medicine for the fecal examinations.

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FLAVOR-MASKING A NEW CALCIUM SYRUP

By William C. Fiedler *

THE important role of calcium in the proper functioning of the body is well recognized. The body is in constant need of the calcium ion and, although an adequate amount can usually be obtained from the diet, in certain abnormal circumstances the dietary sources need to be supplemented. Growing children, for example, need four to six times the adult requirements and increased amounts are necessary during pregnancy and lactation (1). Supplemental calcium is usually taken in tablets and capsules, the gluconate and lactate probably being the most widely used salts in such products. In many instances, due to personal preference or ease of administration, a liquid product may be desirable, but the relatively low solubility of most calcium salts has generally precluded their use in liquid vehicles. Calcium chloride, which has a high solubility in water, is not generally used because it may cause gastric irritation. Two other salts with relatively high solubilities among the calcium compounds are calcium lactate and calcium levulinate. Calcium Lactate N. F. contains 13% available calcium, has a solubility of 1 Gm. in 20 ml. of water, and a usual dose of 5 Gm. (2). Calcium Levulinate N. F. also contains 13% available calcium, has a solubility of 34 Gm. per 100 Gm. of solution at 25° (3), and a usual dose of 1 Gm. (4). The difference in dosage between the two is probably due to a difference in absorption, the calcium content of the levulinate being reported to be unusually well utilized and tolerated (5). Calcium levulinate has been shown to be non-toxic in humans orally, intravenously, and subcutaneously (6). Levulinic acid, a possible decomposition product, produces no toxic effects when ingested by man and has been safely used to acidulate beverages (7).

From the foregoing, it would seem that a liquid calcium levulinate preparation would be desirable from several standpoints. However,

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the only calcium levulinate solutions listed by the 1959 *Drug Topics Red Book* (8) are parenteral products, fourteen in all and usually containing 10% calcium levulinate. The only oral form listed is a 0.5 Gm. capsule.[1]

The greatest disadvantage to the use of calcium levulinate in a liquid oral product is its taste, the drug producing a bitter, salty sensation with a lingering metallic aftertaste. The aim of this particular investigation was to develop a suitable liquid vehicle for calcium levulinate in which the taste of the drug would be effectively masked. A syrup seemed more desirable than an elixir as a vehicle due to the limited solubility of the drug in alcohol and the fact that a heavy syrup would in itself aid in masking the taste. It was decided to use synthetic flavors as masking agents. Such imitation flavors offer several advantages over the natural in the preparation of oral products such as exact reproducibility, ease of preparation, and economy. Furthermore, the intensity of flavor can be increased or decreased without much difficulty, and the products can be colored with a certified coal tar dye to resemble the natural fruit, if necessary (9).

Experimental—The first step in the flavor studies was to determine the preferences of a selected panel toward these flavors. Products containing 12 different flavors in simple syrup were prepared and submitted to a group of 22 students who were asked to denote their flavor preferences. The flavored syrups were tested in groups of 3 and the first choices in each group further rated against each other. An arbitrary value of 6 was assigned to a first choice, 5 for a second choice, etc. Table 1 lists the 12 flavors tested. All contained 0.2% concentration of the flavor in syrup, with the two lemon syrups also containing 0.15% citric acid. The imitation flavors used in this study were the Alva Flavors [2], and the particular flavors listed were selected so as to provide a sampling of various flavor types; i.e., fruity, mint, blended, and other (licorice, maple, and butter caramel). The four top flavors are listed in order of preference, with the percent of total possible score given for each.

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[1] "Solu-Cal Capsules", Carmel and Co., 606 N. Dartmouth, Albuquerque, New Mexico.

[2] van Ameringen-Haebler, Inc., 417 Rosehill Pl., Elizabeth 2, N. J.

TABLE I

FLAVOR PREFERENCES

Alva Flavor	*Choice*	*% Score*
Imitation Butter Caramel No. 3281	1st.	65.9
Sealva Imitation Cherry No. 3352	2nd.	62.1
Sealva Imitation Grape No. 3557	3rd.	61.3
Sealva Imitation Wintergreen No. 3411	4th.	56.0
Imitation Apricot V-3652		
Imitation Licorice No. 3057		
Sealva Lemon Flavor with Other Natural Flavors No. 3335		
Imitation Maple Flavor No. 3424		
Sealva Imitation Tutti Frutti Flavor V-3566		
Imitation Grenadine Extract V-1938		
Sealva Lemon Flavor No. 3373		
Sealva Peppermint Flavor No. 3383		

The three top choices were selected for flavor masking tests with the calcium levulinate[3] itself. The panel taste-testing method used in the present investigation is essentially that of Drommond and DeKay (10). Vials containing 4 ml. samples of the syrups were submitted to a panel of 22 undergraduate students for tasting. Each subject was instructed to rinse his mouth with distilled water and then taste the samples. Fifteen minutes were allowed to elapse between tasting successive samples, and only four samples were tasted on any one day. Medicated syrups and control vehicles were all evaluated in the same manner, the specific syrup sample under evaluation being unknown to the subject in all cases.

A questionnaire was furnished with each sample requesting the following information:

(a) The primary taste sensation—salty, bitter, salty and bitter, or other.

(b) The degree of taste sensation—not at all, slightly, moderately, very, or extremely.

(c) The aftertaste—salty, bitter, salty and bitter, or other.

[3] Chemo Puro Mfg. Corp., 150 Doremus Ave., Newark 5, N. J.

(d) The degree of aftertaste—not at all, slightly, moderately, very, or extremely.

(e) The masking ability of the vehicle—excellent, good, fair, poor, or very poor.

To enable a quantitative comparison, each degree of taste sensation was assigned an arbitrary numerical index, beginning with 1 for "not at all" and proceeding to 5 for "extremely". Likewise, the masking ability of the vehicle was rated from 1 for "very poor" to 5 for "excellent". The total number reported for each degree was multiplied by the numerical index for that degree and the products added together and then divided by the number of subjects reporting. The value obtained was used to compare the relative degrees of taste sensation (Taste Index and Aftertaste Index) and the masking abilities of the various flavored syrups.

Table II tabulates the results of the taste tests with syrups containing 0.2% flavor and 10% calcium levulinate. This concentration of calcium levulinate provides 0.5 Gm. of the drug in each teaspoonful.

TABLE II

RESULTS OF TESTS WITH THE THREE FLAVORS

Flavor	*Taste Index (Strongest: 5.0)*	*Aftertaste Index (Strongest: 5.0)*	*Masking Ability (Best: 5.0)*
None (Drug Only)	4.0	2.6	2.1
Butter Caramel	3.7	2.4	2.4
Cherry	3.6	2.6	2.3
Grape	3.5	2.5	2.6

Although grape appeared to be slightly better than the others in masking ability, all of the products were poor in this respect and the results were too close to enable any definite conclusions to be drawn. Most of the panel members remarked that the flavor seemed to be too weak in all cases. Therefore, additional samples were prepared in which the flavor concentrations were increased to 1.0% and the formulas varied to include adjuncts to modify the tastes and masking abilities of the vehicles. Some of the formulas included the flavor

only, while one series of samples also contained 15% glycerin to enhance flavor and provide "mouth-feel." A third series contained 1% monosodium glutamate (MSG) which has been reported to decrease the aftertaste of the drug besides enhancing flavor (11), while a fourth group contained flavor, glycerin, and monosodium glutamate. Results are tabulated in Table III.

TABLE III

RESULTS OF TESTS WITH MODIFIED SYRUPS

Flavor	*Plain*			*Glycerin*			*MSG*			*Glycerin-MSG*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
Butter Caramel	3.4	2.8	2.6	3.4	2.1	2.8	2.8	2.3	3.1	3.4	2.8	2.4
Cherry	3.3	2.5	2.6	3.1	2.3	3.1	3.3	2.7	2.6	2.8	2.1	2.6
Grape	3.5	2.8	2.8	2.9	1.7	3.6	3.5	2.7	2.6	3.4	2.6	2.5

A—Taste Index (Strongest: 5.0)
B—Aftertaste Index (Strongest: 5.0)
C—Masking Ability (Best: 5.0)

The results show that glycerin exhibits a definite effect in decreasing taste and aftertaste sensations, but that MSG and the glycerin-MSG combinations offer little advantage in this respect. From a consideration of all factors, it can be seen that grape with glycerin was superior to all others. However, the panel still felt that the taste of the drug was too pronounced and the flavors too weak. To overcome these objections, a product was prepared containing 1.5% grape flavor and 20% glycerin in syrup and with the drug concentration reduced to provide 0.5 Gm. in each tablespoonful instead of one teaspoonful. This product was submitted for testing with samples containing the drug with no flavor and flavored samples containing no drug. Results are summarized in Table IV.

TABLE IV

RESULTS OF TESTS WITH THE FINAL GRAPE SYRUP

Syrup Sample	*Taste*	*Aftertaste*	*Masking Ability*
Grape Flavor—No Drug	1.0	1.0	5.0
Drug—No Flavor	3.9	2.0	2.2
Grape Flavor with Drug	2.1	1.3	4.4

The final product had but a slight taste of the drug and a minimum aftertaste, and was judged to be a good to excellent masking agent for the calcium levulinate.

A color was developed for the product by blending coal tar dyes. It was found that 0.3 ml. per 100 ml. of syrup of a mixture of 80% FD & C Red No. 2 and 20% FD & C Blue No. 1 produced an agreeable shade associated with the grape flavor.

One possible source of decomposition in calcium levulinate solutions over a period of time is the formation of calcium carbonate due to decomposition of levulinic acid by oxidation. It has been reported that this difficulty may be overcome by the addition of 0.1 Gm. of ascorbic acid per liter (12). Syrups and solutions containing calcium levulinate in the final concentration were prepared and kept in an incubator for 60 days at 40°C. One syrup and one solution contained 0.01% ascorbic acid and the other samples did not. At the end of 60 days, the syrups had turned dark but no precipitation was seen in any of the samples. Nevertheless, it was thought desirable to include ascorbic acid in the final formula as protection against any oxidation which could occur. Also, a combination of parabens was added as a preservative. The final formula for the product is as follows:

CALCIUM LEVULINATE SYRUP

Calcium Levulinate N. F.	3.34%
Glycerin	20.00%
Sealva Imitation Grape No. 3557	1.50%
Ascorbic Acid	0.01%
Methylparaben	0.25%
Propylparaben	0.15%
Syrup U. S. P. q.s.	

The finished product provides 0.5 Gm. per tablespoonful of calcium levulinate—a soluble, well-utilized, and well-tolerated calcemic—in a palatable, pleasantly-flavored, liquid vehicle.

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THE SYNTHESIS AND PHARMACOLOGY OF ALPHA-METHYL-BENZYL MONOETHANOLAMINE PARA-ETHOXYBENZOATE HYDROCHLORIDE *

By F. Ford Millikan and Seldon D. Feurt †

WHILE the literature is replete with discussions of various local anesthetics, relatively few survive clinical screening. Lack of versatility, irritancy, or acute toxicity mitigates general acceptance of many new local anesthetic agents.

The α-methyl monoethanolamine ester of *p*-ethoxybenzoyl chloride has been prepared and evaluated for pharmacological activity and toxicity.

Experimental

Synthesis. 4.84 Gm. (0.0262 mole) *p*-ethoxybenzoyl chloride and 4.13 Gm. α-methyl-benzyl monoethanolamine (0.025 mole) were dissolved separately in 50 ml. of dry ether. The etheral solution of the alcohol was added at room temperature slowly to the acid chloride with the formation of the ester as an oily mass which collected in the flask. After removing the ether by evaporation, the residue was heated with 200 cc. water and 1 Gm. charcoal, filtered, and allowed to cool: subsequent crystallizations yielded 1.2 Gm. or 13.6% of white crystals with a melting point 181-183° C. (Fisher-Johns). Analysis calculated for $C_{19}H_{24}O_3NCl$: C, 65.22; H, 6.90; N, 4.00; Cl, 10.13; Found: C, 65.46; H, 6.82; N, 4.16; Cl, 10.40. (See Figure I.)

Physical properties:

Solubility at 25° in H_2O	1.125 Gm/100 ml.
Solubility at 25° in Oil	0.0355 Gm/100 ml.
Distribution coefficient oil/water	0.913
pH of saturated solution	4.92
Surface tension of 1% solution	50 D/cm.

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Pharmacological Studies. Acute toxicity—aqueous 1.0 per cent unbuffered solutions of the compound were administered by intraperitoneal injections to adult female albino Webster strain Swiss mice weighing 25 ± 5 Gm. The LD_{50} values were calculated by the method of deBeer (1) with survival after 24 hours considered the end point.

Central nervous system activity was evaluated by the method previously reported by Feurt and LaRocca (2) utilizing the low frequency phase shift thyratron tube activity recording device for gross activity of sixteen female albino Webster strain Swiss mice. Placebo intraperitoneal injections were administered and activity recorded at hourly intervals for a four-hour period daily for ten consecutive days to establish controls. These animals then received by intraperitoneal injection 10 mg/Kg. daily of the ester and the activity performance repeated. While the experiment was designed primarily to show drug effect on the central nervous system activity, the daily observations over a span of two normal estrus cycles will determine anovulatory properties and the predisposition toward tolerance or increased susceptibility.

Local anesthetic properties were evaluated by the methods proposed by Rider (3) utilizing rabbit corneal reflex, frog sciatic nerve, and the conventional human intradermal tests. Effects of sublethal concentrations on blood pressure and respiration in three anesthetized female mongrel dogs were determined by cannulations of carotid and trachea technique, with results recorded on revolving smoked Kymograph paper. Antispasmodic activity on smooth muscle was deter-

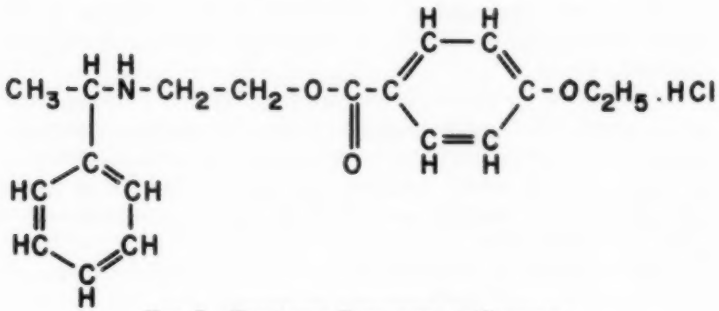

FIG. I—PROPOSED STRUCTURAL FORMULA

mined on guinea pig duodenum by modification of the isolated tissue technique and *in situ* methods proposed by Jackson (4).

Results and Discussion. The LD_{50} of α-methyl-benzyl monoethanolamine *p*-ethoxybenzoate hydrochloride for albino Swiss mice by intraperitoneal injection was determined to be 325 ± 15 mg/Kg. The original aqueous unbuffered solution stored for twelve months in multiple-dose clear glass rubber-stoppered vial was re-evaluated for alterations in toxicity by the same technique, with no significant changes observed.

Effects on the central nervous system as evaluated by the activity recording device by intraperitoneal injection of 10 mg/Kg. resulted in an average depression of gross activity of 48.0 per cent at the end of four hours with the sixteen animals serving as their own controls during the ten-day experimental period. A progressive diminution of effect was observed during the ten consecutive days of drug administration, with an average of 68.8 per cent depression of activity at the end of the first four-hour interval and progressively declining to 38.9 per cent depression at the end of the tenth four-hour interval. No attempt was made to distinguish between the possible local analgetic effect contributing to the suppression of activity rather than true central nervous system depression. Estrus cycles continued normally during the ten-day interval. Large sublethal doses of the local anesthetic agent administered intravenously and intraperitoneally in rats, rabbits, and dogs produced severe convulsive seizures similar to commercial local anesthetic agents. Blood pressure responses in dogs were consistently lowered with doses of 5 mg/Kg. and elevated at larger sublethal concentration. The biphasic physiological responses to this compound are comparable in many respects to the dosage relationship of sedation or convulsion observed in the antihistaminic group.

Spasmolytic properties as evaluated by isolated duodenal tissue and *in situ* studies in guinea pigs gave evidence of potential therapeutic utility. Concentrations of one in one hundred thousand (1:100,000) abruptly arrested normal peristaltic activity and dilutions of one in fifty thousand (1:50,000) prevented the spasmogenic response to parasympathomimetics.

Local anesthetic properties of one per cent unbuffered solution were evaluated and compared to commercial local anesthetics of similar concentration for ability to block sensory impulses and abolish

the withdrawal reflex in frogs and corneal reflex in rabbits. Human volunteers were used to evaluate intradermal injections and ability to block taste receptors. Sensory reflexes in frogs were abolished for ten to twelve minute after application; conjunctival reflexes in rabbits were inhibited for sixty to eighty minutes indicating an intensity of activity equal in duration to commercial local anesthetics. Clinical evaluation in a large southern hospital was completed using approximately one hundred volunteer patients. The local anesthetic agent was administered intradermally in the forearm in concentration of one per cent, total volume of 0.05 cc. Time for onset of action was within three minutes; duration of action was six hours with pain perception to pin prick stimuli as the end point. Erythematous reactions occurred in forty per cent of the individuals treated and localized areas of necrosis with sloughing occurred in approximately ten per cent.

Conclusions

(1) The synthesis and physical properties of α-methyl monoethanolamine *p*-ethoxybenzoate hydrochloride have been described. (2) Toxicity of the new local anesthetic has been determined, and the incidence of undesirable reactions are such as to contraindicate general acceptance as a local anesthetic agent by parenteral administration. (3) Aqueous solutions of this ester are stable with no alteration in toxicity after one year. (4) Evidence indicates a possible utilization as a gastrointestinal spasmolytic.

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SELECTED ABSTRACTS

The Stability of Chloramphenicol in Buffered Solutions. Broadhurst, N., and Wright, S. E. *Australasian J. Pharm. 40:*106 (1959). The authors evaluated the stability of chloramphenicol in solution, varying the pH, the buffer used, the concentration of chloramphenicol, and the method of sterilization.

Using a borate buffer at a pH of 6, 7, and 8, the authors found that the percentage of decomposition was greatest at pH 8, less at pH 7, and least at pH 6. This relationship applied whether the solution was autoclaved at 115° C. for 30 minutes or heated at 100° C. for 30 minutes. Decomposition was much greater with autoclaving than with boiling. For example, at a pH of 8 the autoclaved solution of a 0.5 per cent concentration showed a decomposition of 22 per cent while the boiled solution showed a decomposition of 7 per cent. For the same solution at a pH of 6, the decomposition was 5.2 and 3.2 per cent, respectively. A solution having a concentration of 0.25 per cent and a pH of 6, after boiling, showed a decomposition of only 1.2 per cent.

In a comparison of vehicles, the authors reported that a 0.25 per cent solution of chloramphenicol boiled at 100° C. for 30 minutes showed a decomposition of 5.2 per cent at a pH of 6 in a phosphate buffer, of 1.6 per cent at a pH of 7 in distilled water, and of 1.2 per cent in a borate buffer at pH 6.

It was concluded that chloramphenicol should be dispensed in a borate buffer at a pH of 6 and should be sterilized by heating at 100° C. for 30 minutes. The following formula was suggested:

Chloramphenicol	0.50 Gm.
Sodium Borate	0.15 Gm.
Boric Acid	4.20 Gm.
Preservative, q.s.	
Distilled Water, to make	100.00 ml.

The chloramphenicol should be dissolved in the buffer solution at 95-98° C. and then cooled quickly.

Comparative Diuretic Effects of Chlorothiazide and Mercaptomerin. Fairweather, M. J., Lewis, J. M., Chapman, D. W., and Ford, R. V. *Postgrad. Med. 25:209* (1959). The orally administered diuretic chlorothiazide and the parenterally administered diuretic mercaptomerin were given to 20 edematous male patients who had cardiac disease or cirrhosis. The patients were at rest in bed and they were fed a diet which contained 800 mg. of sodium with a controlled fluid intake of 3000 ml. a day. Comparative therapy was planned on the basis of a twelve-day cycle. The first three days were control; during the next three days, therapy with one drug was given; the next three days were control; and, during the last three days, the second drug was administered. The dosage of chlorothiazide was 2000 mg. orally each day for three days and that for mercaptomerin was 2 ml. parenterally each day for three days. The values for the sodium, potassium, and chloride in the serum and the carbon dioxide combining power were determined once each period. The volume of urine excreted and the sodium content were determined for each 24 hour period. The weight of the patient was also recorded each day.

Chlorothiazide has been shown to act by inhibiting the reabsorption of sodium and chloride ions in approximately equal amounts (a saluretic agent). Potassium ions are excreted to a smaller degree than sodium, and bicarbonate excretion is minimal. Mercaptomerin also prevents reabsorption of sodium and chloride ions. It produces no significant potassium loss while bicarbonate excretion is temporarily suppressed.

The data from this study confirmed previous findings that orally administered chlorothiazide is a more potent saluretic agent than intramuscularly administered mercaptomerin. The tendency of both drugs to produce disurbances in serum biochemical architecture is approximately equal. A mild hypokalemia was observed in 2 of the 20 patients, which could easily be controlled by diet and proper spacing of the dosage of the diuretic. The most common electrolyte disturbance was hypochloremic alkalosis, but this could be controlled by the administration of ammonium chloride. An important observation of the authors was that, when the body was depleted of sodium and water by the administration of one diuretic, the response of the second diuretic was spuriously low unless the body store of sodium was permitted to return to control level before the second drug was administered.

Factors Affecting the Absorption of Local Anesthetics. Campbell, D., and Adriani, J. *J. A. M. A. 168*:873 (1958). Factors which determine the rate and amount of absorption of local anesthetics were studied in dogs and by parallel clinical studies where possible. The drugs used were cocaine, tetracaine, procaine, and benzocaine. Concentrations obtained in the blood were determined.

The authors recorded many interesting findings. It was found that a rapid intravenous injection produced a rapid peak in blood level but that the same dose injected over a period 20 times longer produced no significant blood level. Infiltration gave blood levels that were detectable but not measurable. Topical application to the mucous membranes of the pharynx and trachea gave blood levels with somewhat lower peaks but otherwise comparable to rapid intravenous injections. It was also found that the absorption following topical application was a function of the total dosage rather than of the concentration of the solution applied.

Vasoconstrictors, such as epinephrine and arterenol, did not retard absorption from the mucous membranes. A ten per cent solution of cocaine, which has a vasoconstrictor effect of itself, showed approximately the same blood level as an equivalent weight of cocaine applied to mucous membranes as a 4 per cent solution. However, the vasoconstrictors were effective in retarding absorption following perineural or subcutaneous injections.

Detectable blood levels were obtained following the application of local anesthetics to broken or abraded skin and from the raw surfaces of third degree burns. There was no absorption from the surfaces of first or second degree burns.

The free bases of local anesthetics were absorbed almost as rapidly from mucous membranes as were the salts, provided the drugs were in an aqueous medium. When the drugs were incorporated in oily vehicles, blood levels were not detectable. Bases incorporated in a water-soluble ointment base gave drug levels similar to those resulting from the application of aqueous suspensions to mucous membranes. Hyaluronidase was found to facilitate the absorption of injected local anesthetics but not that from topical application.

The mode of topical application of local anesthetics is often debated, according to the authors. With regard to anesthetizing the nasal and pharyngeal mucosa, nebulization of the solution is the only

effective mode of application. However, the authors warned that careless use of a spray can lead to overdosage.

The authors emphasized that the most important precaution to be followed to avoid overdosage of the local anesthetics is to limit the dose employed. The anesthetist must also be well-informed as to the factors that may affect absorption. In general, for perineural injection or infiltration, the dose of procaine should be limited to 1 Gm., tetracaine to 100 mg., piperocaine hydrochloride to 1 Gm., lidocaine hydrochloride to 0.5 Gm., hexylcaine hydrochloride to 1 Gm., and chloroprocaine to 1 Gm.

The Antibacterial Activity of Thiostrepton Against Certain Pathogens. Kelly, J., Schraft, W. C., Kutscher, A. H., and Tuoti, F. *Antibiot. and Chemother. 9*:87 (1959). Thiostrepton is a newly developed crystalline antibiotic derived from a *Streptomyces* species. Previous studies had showed that it was active against many gram positive microorganisms but relatively inactive against gram negative bacteria and fungi. For most organisms inhibited by thiostrepton, the minimal inhibitory concentration was in the vicinity of 0.03 to 0.06 mcg./ml.

The authors obtained 203 strains of bacteria from clinical sources and studied the antibacterial activity of thiostrepton by the disc sensitivity method. The strains studied included six of *Pseudomonas aeruginosa,* three anaerobic varieties, eight *Proteus* species, five *Streptococcus viridans* types, ten non-hemolytic streptococci, seven *Aerobacter aerogenes,* twenty-three *Staphylococcus albus,* thirty *Escherichia coli,* eighty-two *Staph. aureus,* fifteen combination isolates of *Streptococcus faecalis* and *E. coli,* seven combination isolates of *Staph. albus* and *E. coli,* and seven miscellaneous organisms.

Based upon the presence or absence and the magnitude of zones of inhibition around the discs, the authors found that 80 of 82 strains of *Staph. aureus,* 9 of 10 strains of non-hemolytic streptococci, all 23 strains of *Staph. albus,* all 5 strains of *Streptococcus viridans* type, and all 3 anaerobic varieties were either very sensitive or moderately sensitive to thiostrepton. None of the strains of *Ps. aeruginosa, Proteus* species, *A. aerogenes,* and *E. coli* were sensitive to the antibiotic. The authors concluded that these findings suggested that thiostrepton should be given clinical trial in the treatment of gram positive infections.

Vitamin A, An Aid to the Clearing of Warts. Kuhn, B. H. *South. Med. J. 52:*211 (1959). The oral administration of 50,000 to 200,000 units of vitamin A a day in conjunction with the local application of a caustic preparation increased the rate at which a complete cure from multiple warts was obtained. Complete cures were obtained in 75 per cent of 90 patients treated with the combined therapy as compared with 25 per cent, previously, with only topical treatment. In addition to those patients who showed a complete cure, most of the other patients showed improvement. Four recurrences were encountered, but all four of these patients responded with a complete cure when therapy was resumed.

The period during which therapy was continued varied from 1 week to about 6 months. The age of the patients varied from 3½ to 56 years. The warts had existed for periods up to about 5 years.

The author noted that the warts gradually decreased in size and finally disappeared or gradually loosened and dropped off without leaving any residual scar. There appeared to be no correlation with the dosage required and the type of wart. Neither was there correlation between the number or duration of warts and the duration of treatment required to effect a cure.

The author became interested in the use of vitamin A in the treatment of warts because of the observation that warts spontaneously disappeared in a number of patients who were receiving vitamin A for acne.

The Ultra-violet Absorption Characteristics of Rescinnamine in Solution. Joint Comm. of The Pharm. Soc. of G. B. and The Soc. for Analyt. Chem. on Methods of Assay of Crude Drugs. *J. Pharm. & Pharmacol. 11:*211 (1959). A method had been described for the assay of reserpine and rescinnamine in rauwolfia depending upon the separation of these two bases from others present, followed by hydrolysis to trimethoxybenzoic acid and trimethoxycinnamic acid, respectively. The two acids were then determined in solution in chloroform by an ultra-violet absorption method. However, it was found that there was a wide discrepancy in the results obtained from different laboratories for rescinnamine and trimethoxycinnamic acid.

A study revealed that exposure to daylight produced a change in the wave length of maximum absorption and in the extinction co-

efficients of solutions of trimethoxycinnamic acid and of rescinnamine. Using different solvents, it was found that maximum changes occurred after about 24 hours exposure to daylight.

In order to determine whether or not these changes also brought about changes in the pharmacological activity of rescinnamine, solutions exposed to daylight and then assayed to be sure that the spectrophotometric changes had occurred were studied pharmacologically. No differences could be observed between the control and test solutions as to their pharmacological activity on the blood pressure of anaesthetised cats and on certain vasopressor reflexes.

The report concluded, therefore, that this problem is a purely analytical one. It was concluded that the ultra-violet absorption characteristics of rescinnamine could not be used as a basis for the determination of the alkaloid unless exposure of solutions to daylight until the ultra-violet absorption characteristics became constant could provide uniform conditions for subsequent spectrophotometric evaluation.

The Antianemic Effectiveness of a Ferric Chelate Compound. Lapinleimu, K., and Wegelius, R. *Antibiot. Med. and Clin. Ther. 6:*151 (1959). The therapeutic effectiveness of orally administered ferric sodium ethylenediaminetetraacetate in infants and children with hypochromic anemia was studied by the authors and compared with ferrous gluconate.

In the first study reported by the authors, 10 infants and children were given the ferric chelate compound in a daily dose of 152 mg. and 8 patients were given ferrous gluconate in a daily dose of 132 mg. The iron content of the two preparations was equivalent. Fasting serum iron levels were determined prior to the administration of the iron compound and serum iron levels were again determined one and three hours after oral therapy had been given. The results indicated that the trivalent ferric chelate compound was absorbed readily and that the rise in the serum iron values was of the same magnitude as that obtained with the bivalent ferrous gluconate. The authors postulated that the trivalent iron may be rapidly reduced in the stomach and upper intestines to a soluble and ionizable bivalent iron compound.

In another study, ferric sodium ethylenediaminetetraacetate was used routinely in a hospital for the treatment of hypochromic anemia

in 402 infants and children. Infants received 19 mg. and older children, 38 mg. two to three times a day. Routine observation of the patients and serum iron determinations in some cases led the authors to conclude that the antianemic response from this compound was as good as had been obtained previously from the use of bivalent iron compounds. In addition, the incidence of gastrointestinal side effects was very small—only 7.2 per cent of the patients.

The authors pointed out that ferric sodium ethylenediaminetetraacetate has a decisive practical advantage in that the strong linkage of iron in the complex enables the preparation of aqueous solutions free from ionized iron. Therefore, palatable pharmaceutical solutions that do not discolor or otherwise harm the teeth can be readily prepared.

Comparative Studies of Demethylchlortetracycline With Chlortetracycline and Tetracycline. Sweeney, W. M., Hardy, S. M., Dornbush, A. C., and Ruegsegger, J. M. *Antibiot. & Chemother. 9*:13 (1959). The new antibiotic dimethylchlortetracycline, which differs from chloretetracycline in the absence of a methyl group on the 6 position of the tetracycline molecule, was compared with chlortetracycline and tetracycline with regard to absorption and excretion. Sixteen healthy male subjects were given a single oral dose of the antibiotic under test on a fasting stomach. Blood levels of the antibiotics were determined at zero, one, three, and six hours and the total excretion in the urine was determined over an eight hour period. During the study period, each subject received each of the antibiotics, appropriately spaced by at least 72 hours.

The authors found that tetracycline yielded the highest blood levels at one, three, and six hour intervals. Chlortetracycline and demethylchlortetracycline showed almost identical blood levels at the one and three hour intervals but the demethylated compound showed a higher level at the six hour interval. Further studies showed that demethylchlortetracycline produced demonstrable antibacterial activity in the serum of all six subjects given a single dose of 500 mg. after 120 hours. No activity was present in the serum of subjects given tetracycline and chlortetracycline after 72 hours. This persistent serum antibiotic activity after the administration of demethylchlortetracycline has been shown to be due, at least in part, to a reduced rate of clearing by the kidney. It was found that demethylchlortetra-

cycline was cleared by the kidney only 43 per cent as rapidly as tetracycline.

This new demethylated compound has also been found to exhibit striking stability to acids and alkalies as compared with its methyl homologues. The new antibiotic is well tolerated and has a low order of toxicity. It is effective against the same general range of bacteria as the other tetracyclines.

The Antifilarial Activity of Certain New Quaternary Ammonium Compounds. Hawking, F., and Terry, R. J. *J. Pharm. and Pharmacol. 11*:94 (1959). Several new series of quaternary ammonium compounds have been developed and tested for their antifilarial activity. These include eicosane 1:20-bis-quinolinium, -isoquinolinium, -7-aminoisoquinolinium, -4-aminoquinaldinium, and -4-aminocinnolinium abbreviated; respectively, BQn, BIQn, BAIQn, BAQDn, and BACn, where n is equal to the number of methylene groups in the chain.

Selected compounds were tested for antifilarial activity against *Litomosoides carinii*, the filarial parasite of the cotton rat. The results showed that some of the compounds possess considerable antifilarial activity. Most promising of these were (BIQ 20) eicosane 1:20-bis (isoquinolinium iodide) and (BAC 20) eicosane 1:20-bis(4-aminocinnolinium iodide). The index of activity (LD_{50} in mice/minimum effective dose in cotton rats) was 18.7 for BIQ 20 and 39 for BAC 20. Although this index of activity measurement was not considered completely satisfactory, it did provide a reasonable estimate of the therapeutic value of a compound during preliminary screening.

The compounds apparently had a direct filaricidal action upon the adult worms, although the microfilariae were comparatively unaffected. The most susceptible parts of the adult female worms seemed to be the developing embryos and oöcytes, probably because these tissues have the highest metabolic turnover in the worm.

Although these compounds are toxic to the host as well as filaricidal, there was a fair margin between the minimum curative dose and the maximum tolerated dose for the two most promising compounds. The authors concluded that these preliminary results indicated that BIQ 20 and BAC 20 deserved further study in larger animals and man. However, they acknowledged that the ultimate utility of these compounds cannot yet be predicted.

Preliminary Observations on the Use of DBI as an Oral Hypoglycemic Agent. Weller, C., and Macaulay, A. *J. Am. Geriat. Soc. 7:*128 (1959). The hypoglycemic agent N-beta-phenethyl-formamidinyliminourea (DBI) was given to a group of 42 unselected patients with diabetes mellitus of a few months duration to as long as 44 years. The patients varied in age from 24 to 80 years. In none of the patients had it been possible to control the diabetes with diet alone.

The dosage of insulin was discontinued or lowered until glycosuria occurred. DBI was then started with a dosage of 25 mg. three times a day with meals and slowly increased until normoglycemic blood levels were reached, or nausea and vomiting occurred. The dose of insulin was then gradually lowered, and the dose of DBI increased, until the desired blood sugar levels were established and/or glycosuria was controlled.

The patients were considered to have responded to therapy if the blood sugar concentration was decreased by 30 per cent or more and/or glycosuria was decreased by 50 per cent or more from levels achieved with previous therapy or if the insulin requirement was decreased by 50 per cent or more. Based upon these criteria, 53 per cent of the patients responded to therapy with DBI. An additional 12 per cent responded well but the side effects of nausea and/or vomiting were so severe that therapy had to be discontinued. The latter were not considered as having been successfully treated. Of the successfully treated patients (22), insulin was completely replaced in 16.

These preliminary observations indicated that DBI was an effective agent in the control of diabetes mellitus, not only in the older patient with mild diabetes, but also in some patients with insulin-deficient diabetes. These included juvenile diabetes, severe diabetes in adults in whom large doses of insulin were required, and mild diabetes in patients who had not shown improvement with other oral hypoglycemic agents. The authors concluded that DBI appeared to provide advantages other than the mode of administration. Although DBI may make the initial regulatory task more difficult, it widens the spectrum of regulatory agents and, thus, has a significant place in the treatment of diabetes.

BOOK REVIEWS

Text Book of Microbiology, Fourth Edition. Kenneth L. Burdon. 645 pp. including index. The Macmillan Company, New York, N. Y., 1958. Price: $5.75.

The purpose of this text is not to provide technical training for microbiologists but to provide the basis for an understanding of the phenomena of microbic life and of host microbe interrelationships.

Part One of the text is an introduction to the basic elements of microbiology. Part Two discusses sources and modes of infection, sterilization and disinfection, and chemotherapy. Part Three deals with infection, resistance of the body, and hypersensitivities. Part Four presents an overview of the microbiology of important infectious diseases.

The text is recommended to the student approaching the subject for the first time since this is a book which, despite the complexities of subject matter, remains understandable and interesting.

LEO B. JORDAN

Physiology of Spinal Anesthesia. N. M. Greene. xi + 195 pp. The Williams and Wilkins Co., Baltimore 2, Maryland, 1958. Price: $6.00.

Since its introduction sixty years ago, spinal anesthesia has passed through phases characterized by overly enthusiastic acceptance followed by phases of complete rejection. This monograph has been written to supply objective information about the physiological effects of spinal anesthesia.

Each chapter deals with the effects of spinal anesthesia on a different system of the body. There is also an excellent section devoted to obstetrical applications.

Included in the text are graphs and tables summarizing the effects of this method of anesthesia, and a complete bibliography.

This book would, therefore, serve as an excellent reference for the physiologist, pharmacologist, anesthesiologist, and surgeon in their comprehension and application of the methods of spinal anesthesia.

EUGENE E. VOGIN

Ion Exchange Resins, Second Edition. Robert Kunin. xiii + 466 pp. John Wiley and Sons, Inc., New York 16, N. Y., 1958. Price: $11.00.

Due to the abundance of literature in the ion exchange field since this book was first published eight years ago, a second edition was necessarily desirable. Dr. Kunin has done an outstanding job of sifting the bulk of the material in this field and presents it in an easily digested form.

The first fourteen chapters range in substance from the history, theory, and synthesis of ion exchange resins to their uses in the laboratory and industry for deionization, purification, catalysis, and analysis. The final three chapters dealing with the study, stability, and economics of using the resins are of especial interest to those uninitiated in the use of ion exchange materials. With the widespread use of these resins in the pharmaceutical industry, this book should be valuable to everyone engaged in the production of medicinals.

A. R. GENNARO

Schizophrenia. M. Sakel. vii + 335 pp. Philosophical Library, Inc., New York 16, N. Y., 1958. Price: $5.00.

This is a definitive work on a relatively new frontier in medicine from the man who opened it to the world and was, until his recent death, its foremost authority.

Schizophrenia has long been the greatest single problem in psychiatry and mental hospitals. But Dr. Sakel's discovery and development of the treatment that bears his name has revolutionized medicine's attitude toward endogenous psychoses and has given new life and hope to thousands of mental patients.

Part I investigates the "theoretical" background: the history and description of schizophrenia, the causes and classifications of the illness—symptoms, diagnosis, and prognosis. Part II is devoted to Dr. Sakel's own clinical description of his treatment with full medical data and detailed records of many case histories.

This book correlates, analyzes, and presents many of the ideas relating to schizophrenia and, as such, serves as an excellent reference for the interpretation and understanding of this condition.

EUGENE E. VOGIN

Reproduction and Infertility. III Symposium. Edited by F. X. Gassner. vii + 273 pp. Pergamon Press Inc., 122 E. 55th St., New York 22, N. Y., 1958. Price: $6.50.

This publication provides a written account of the proceedings of the Third Symposium on Reproduction and Infertility held in the summer of 1957.

The scope of the material included in this text ranges from the effects of radioactive fallout on humans to diseases of the reproductive system in male and female, ovarian physiology, steroid physiology and therapy, the general problems of reproduction, and semen metabolism and artificial insemination.

Of special interest are the accounts of the panel discussions held at the conclusion of each section meeting.

The completeness of the references and the index makes this text an excellent reference source for the reproductive system.

EUGENE E. VOGIN

Thérapeutique et Spécialités Pharmaceutiques. Paul Guilleman. 886 pp. G. Doin & Cie, Paris, 1957. Price: 3.300 fr. (approx. $6.60).

The purpose of this book is to simplify the task of the practicing physician of keeping informed about the most recent and most effective medication for specific cases. The author adopted an alphabetical classification of diseases, omitting those which are not applicable to practical therapy.

Each chapter is a separate entity headed by the name of the disease to be discussed. General and specific treatments are suggested This provides the physician with a choice of treatment for a specific case. The innovation which makes this book very unique and practical is the listing of the most important specialties for use in a given disease. Such a "repertorium" follows each chapter. The physician is free to choose among the different suggested treatments and the medication.

In an era in which the practicing physician is overwhelmed by the number of new medicaments and finds it difficult to keep posted and informed, this ready reference book is a valuable aid in orienting him toward the proper course of treatment.

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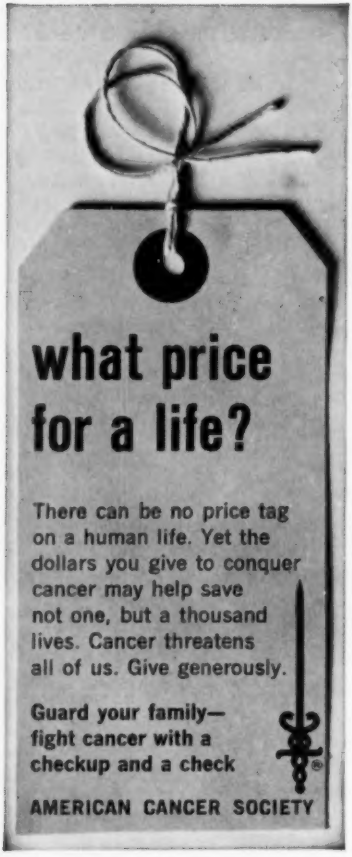
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